ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa053

REVIEW
Drug Treatment

Antithrombotic therapy in patients undergoing transcatheter aortic valve replacement: the complexity of the elderly

Leonardo Bencivenga [1,2], Immacolata Sepe[1], Maria Emiliana Palaia[1], Klara Komici[3], Graziamaria Corbi[3], Brunella Puzone[1], Michele Arcopinto[1], Antonio Cittadini[1], Nicola Ferrara[1,4], Grazia Daniela Femminella[1,5], and Giuseppe Rengo [1,4]*

[1]Department of Translational Medical Sciences, University of Naples "Federico II", Via Sergio Pansini 5, Naples 80131, Italy; [2]Department of Advanced Biomedical Sciences, University of Naples "Federico II", Via Sergio Pansini 5, Naples 80131, Italy; [3]Department of Medicine and Health Sciences, University of Molise, Via Francesco De Sanctis 1, Campobasso 86100, Italy; [4]Istituti Clinici Scientifici Maugeri SPA, Società Benefit, IRCCS, Istituto Scientifico di Telese, Via Bagni Vecchi 1, Telese Terme 82037 (BN), Italy; and [5]Department of Medicine, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

Received 4 May 2020; revised 3 July 2020; editorial decision 7 August 2020; accepted 12 August 2020

Along with epidemiologic transitions of the global population, the burden of aortic stenosis (AS) is rapidly increasing and transcatheter aortic valve replacement (TAVR) has quickly spread; indeed, it is nowadays also employed in treating patients with AS at intermediate operative risk. Nonetheless, the less invasive interventional strategy still carries relevant issues concerning post-procedural optimal antithrombotic strategy, given the current indications provided by guidelines are not completely supported by evidence-based data. Geriatric patients suffer from high bleeding and thromboembolic risks, whose balance is particularly subtle due to the presence of concomitant conditions, such as atrial fibrillation and chronic kidney disease, that make the post-TAVR antithrombotic management particularly insidious. This scenario is further complicated by the lack of specific evidence regarding the 'real-life' complex conditions typical of the geriatric syndromes, thus, the management of such a heterogeneous population, ranging from healthy ageing to frailty, is far from being defined. The aim of the present review is to summarize the critical points and the most updated evidence regarding the post-TAVR antithrombotic approach in the geriatric population, with a specific focus on the most frequent clinical settings.

Keywords Elderly • Aortic stenosis • TAVR • Antithrombotic therapy • Atrial fibrillation • Chronic kidney disease • Geriatric syndromes • Autonomic dysfunction • COVID-19

Introduction

Aortic stenosis (AS) represents the most common valvular heart disease in Europe and North America, with a steadily growing prevalence due to the ageing population.[1] Indeed, although the predictable variability among data derived from epidemiological studies and the slight contribution of bicuspid aortic valve and congenital forms, this condition particularly affects elderly patients. It is estimated that about 5% of the population at age 65 suffers from AS and it is becoming increasingly frequent in clinical practice.[2]

Calcific degeneration of valve structure constitutes the most common cause of AS in the Western world, whereas rheumatic AS still remains the main aetiology in developing countries.[3] The pathophysiological mechanisms leading to valve stenosis are considered to be similar to those involved in the development of atherosclerotic plaques, with emerging therapeutic implications.[4] Actually, advanced age, male gender, dyslipidaemia and systemic inflammatory status represents shared risk factors between coronary artery disease and AS.[5] Initially, aortic degeneration insidiously progresses, then symptoms' onset is paralleled by a fast worsening of valvular stenosis and calcifications. The symptomatologic manifestations, including breathlessness, angina, palpitations and syncope, are crucial for the assessment of aortic valve replacement therapy, though the heterogeneity of clinical presentation also poses controversies in approaching asymptomatic patients with instrumental evidence of severe AS.[6]

* Corresponding author. Tel: +39 0817462339, Fax: +39 0817462339, Email: giuseppe.rengo@unina.it

Transcatheter aortic valve replacement (TAVR) constitutes the therapy of choice for patients with symptomatic severe AS who are not suitable for surgical aortic valve replacement (SAVR), especially elderly patients, available for transfemoral access, at increased surgical risk [Society of Thoracic Surgeons (STS) or EuroSCORE II ≥4% or logistic EuroSCORE I ≥ 10%], or presenting other risk factors, including limited mobility, severe comorbidities, frailty, porcelain aorta, or sequelae of chest radiation.[1]

The present review aims to summarize the most updated evidence regarding the management of the geriatric population undergoing TAVR, especially focusing on the antithrombotic treatment strategies in specific clinical settings.

Current definitions and indications

According to European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for the management of valvular heart disease, severe AS is currently defined as aortic valve area <1.0 cm^2 and/or a mean transaortic pressure gradient >40 mmHg and/or a peak aortic jet velocity (V_{max}) >4 m/s, together with evaluation of flow rate, ventricular function, size and wall thickness.[7] Transthoracic and/or transoesophageal echocardiography constitute the diagnostic gold standards, with exercise testing recommended for unmasking asymptomatic patients.

Since the first procedure performed in 2002, TAVR was supported by scientific evidence, showing superiority or non-inferiority compared to SAVR. Moreover, TAVR has rapidly spread and it is nowadays also employed in treating patients with intermediate operative risk. The decision-making process in elderly patients requires tailored considerations and should include a comprehensive geriatric evaluation. Indeed, despite unquestionable advantages, TAVR is burdened by many relevant complications, such as paravalvular regurgitation, aortic injury, heart block, vascular access haemorrhages, and thrombosis/embolization of the prothesis.[3]

Ischaemic/embolic and bleeding complications are strongly related to mortality, thus the optimal antithrombotic approach after TAVR still remains debated. Despite no strong evidence exists yet, dual antiplatelet therapy (DAPT) is warranted for the first 3–6 months, followed by single antiplatelet therapy (SAPT) lifelong.[1] A recent analysis of 16 694 patients undergoing TAVR showed an increase in bleeding risk with DAPT as compared to SAPT without any significant difference regarding 1-year mortality, myocardial infarction, or stroke.[8] The Aspirin Versus Aspirin plus Clopidogrel Following Transcatheter Aortic Valve Implantation (ARTE) trial confirmed DAPT to increase the rate of complications compared to SAPT.[9] Accordingly, ESC guidelines for the management of Valvular Heart Disease states that SAPT may be the preferred choice compared to DAPT in patients with high risk of bleeding (Class IIb), especially for elderly patients with several comorbidities.[1]

In this scenario, the management of elderlies undergoing TAVR is particularly complex: older patients suffer higher thromboembolic and bleeding risks, comorbidities and various degrees of disability and dependency, which make the correct choice of antithrombotic strategy after TAVR particularly challenging[10] (*Figure 1*).

Key points: DAPT prescription should be indicated for the first 3–6 months after TAVR, followed by SAPT lifelong. Consider SAPT in high bleeding risk (e.g. frail elderly, several comorbidities).

Cerebrovascular complications in TAVR

Cerebrovascular complications in patients undergoing TAVR, whose rates appear to be relatively unchanged over time although improvements in device technology, are very relevant due to great impact on both outcomes and quality of life.[11] The pathophysiology underlying cerebrovascular injuries typically comprises embolic, haemorrhagic, and atherothrombotic events.[12] Neurological complications mainly occur in the periprocedural period and they are primarily related to valve positioning, deployment, and valvuloplasty balloon.[13] Indeed, a fertile substrate for thrombogenicity is constituted by the presence of tissue factor and thrombin on calcific native aortic valve, whose manipulation in the context of the procedure may facilitate embolization. Furthermore, blood flow turbulence can be generated by the mechanical interaction between the prosthesis and the native valve, and the device itself may induce platelet aggregation and coagulation cascade activation. This scenario is intuitively aggravated in the elderly by the frequent concomitance of chronic conditions [e.g. atrial fibrillation (AF), hypertension, diabetes] which represent risk factors for ischaemic and embolic events *per se*.[14]

The Placement of Aortic Transcatheter Valves (PARTNER) trial has demonstrated that TAVR improved 1-year survival compared to medical therapy, but it was associated with higher rates of stroke at 30 days.[15] The PARTNER-2 trial, by randomizing 2032 intermediate surgical risk patients with severe AS to TAVR or SAVR, has shown comparable 2 years incidence rates of death from any cause and stroke, whose incidence was similar in the acute phase and in the follow-up.[15] The PARTNER-3 trial has enrolled a thousand low surgical risk AS patients to either SAVR or TAVR, resulting in significant improvement in the occurrence of post-TAVR stroke, both at 30 days and 1 year.[16]

Given the above-mentioned high thromboembolic risk, anticoagulation is required during TAVR. Even if practice patterns widely vary and the current indications are mainly based on expert consensus rather than on evidence from randomized clinical trials, unfractionated heparin regimen is preferred to direct thrombin inhibitors.[17,18] Moreover, in order to prevent celebral embolization, multiple protection devices, classified as filtering and diversion systems, have been developed and employed, but their effectiveness is still debated.[19]

Interestingly, besides clinically apparent strokes, neuroimaging studies have shown that more than two-thirds of patients experience post-TAVR multiple silent ischaemic-embolic lesions, spread across both hemispheres.[20] A recent multicentre study on 3750 TAVR patients with mean age of 80 ± 8 years revealed that age, history of cerebrovascular disease, higher aortic gradient, periprocedural stroke, and the lack of anticoagulation prescription were related to augmented risk of late cerebrovascular events.[21] Controversial results emerged regarding the clinical implications and prognostic

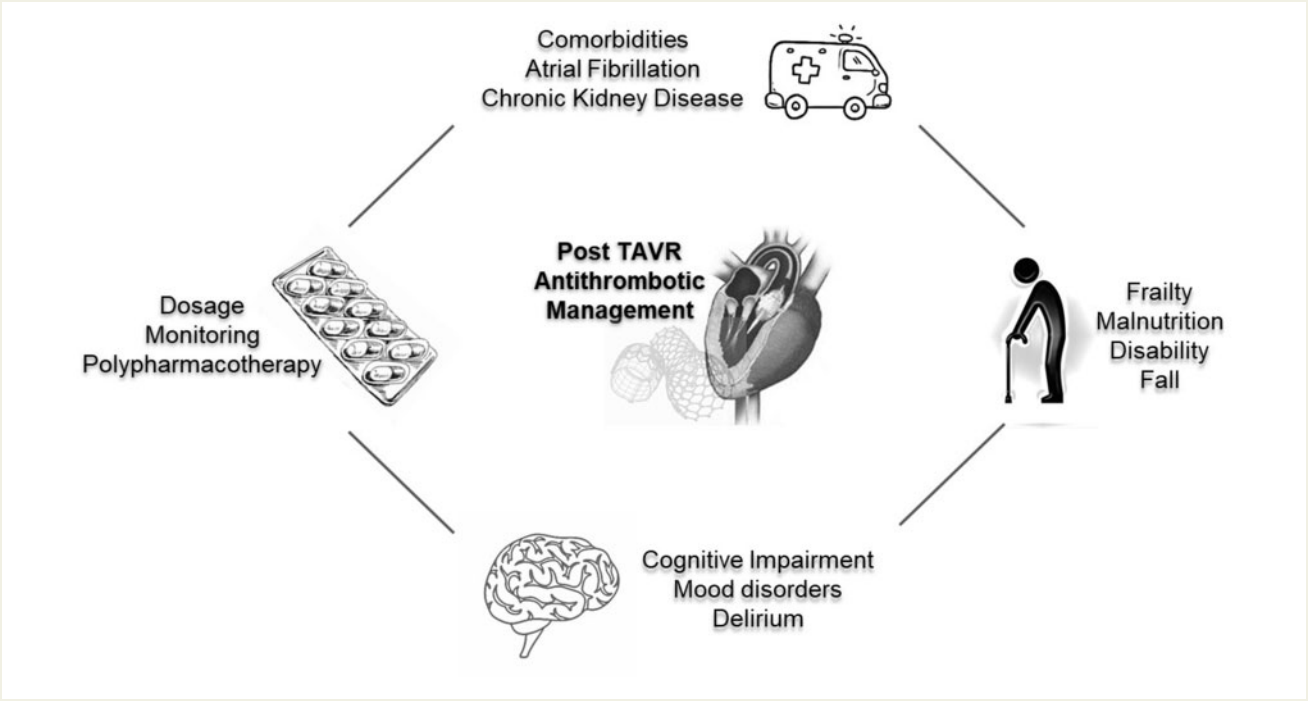

Figure 1 The complexity of antithrombotic strategy after TAVR in elderly. Real-life geriatric patients suffer comorbidities and various degree of disability, which carry many issues concerning the correct choice of post-procedural optimal antithrombotic strategy. Cognitive impairment and polypharmacotherapy concur to make the balance between concomitant thromboembolic and bleeding risks even more unstable. TAVR, transcatheter aortic valve replacement.

role of these subclinical injuries, and even their association with cognitive decline is largely debated.

Key points: unfractionated heparin should be preferred for anticoagulation during TAVR, even to reduce periprocedural cerebrovascular complications. Protection devices need to be further investigated.

Antithrombotic therapy in patients with atrial fibrillation

AF constitutes the most frequent arrhythmia worldwide, and its prevalence exponentially increases with age.[22] It also represents one of the most relevant comorbidities in patients undergoing TAVR. Indeed, pre-existing AF has been documented in more than one-third of the population undergoing the percutaneous procedure, whereas new-onset AF (NOAF) occurs in about 8% of patients.[23] Stroke represents a major complication after TAVR with up to 7% of patients developing cerebral ischaemic event within the first 12 months, whilst periprocedural stroke, occurring in the first 24 h, seems to be related to prosthetic valve leaflet embolization.[24] Accordingly, recent data from registries indicate that the average time from valve replacement to stroke is 181 days, allowing to speculate that the first 6 months of higher risk corresponds to the time necessary for the complete endothelialization of the prosthetic valve.[25]

However, post-procedural stroke may be also associated with comorbidities, with pre-existing rhythm disturbance and NOAF being the most relevant. More in detail, NOAF has been related to ischaemic events in the first 30 days (subacute stroke) and pre-existing AF up to 1 year (late stroke) after the procedure.[26,27] According to other evidence, patients with stroke often develop NOAF almost immediately after TAVR[28] and it has been related to a higher risk of early stroke compared to pre-existing AF.[29] Of note, it is important to underline that NOAF occurrence is even higher after SAVR than TAVR, although constituting a side effect of both approaches.[30] Furthermore, the diagnosis of NOAF can be particularly insidious, especially in paroxysmal rhythm disturbance lasting less than 30 s, consequently, subclinical NOAF patients suffer less chance to start anticoagulant therapy than patients with pre-existing AF.[31] This clinical setting is further complicated in elderly patients, which are often asymptomatic for rhythm disturbances. Further data indicate that subclinical NOAF episodes are more common than overt NOAF after TAVR, thus suggesting that prolonged rhythm surveillance may be useful to prevent thromboembolic events.[32] Besides NOAF, pre-existing AF also enhances periprocedural cardiac complications occurrence.[33] AF constitutes one of the main indication to anticoagulation therapy: the most recent ESC guidelines for the management of AF indicates oral anticoagulant (OAC) therapy for all patients with paroxysmal, persistent or permanent AF presenting a valuable thromboembolic risk assessed through CHA_2DS_2-VASc score (≥2 in men and ≥3 in women).[34]

Conditions that require the use of antiplatelet therapy are also very frequent among TAVR patients: a consistent proportion (40–70%) of the 2% of patients presenting myocardial infarction within 1-year post-TAVR suffered from chronic coronary artery disease years before the valve replacement procedure,[35] thus already taking antiplatelet therapies for appropriate prevention of acute ischaemic events.[27] Similarly, in AF patients undergoing TAVR, antiplatelet therapy should also be prescribed in addition to OAC despite these

therapeutic approaches exponentially increase the risk of major bleeding, which should be carefully weighed. According to ESC guidelines, empirical treatment recommendations include aspirin or thienopyridine in addition to OAC life-long in AF patients, but this therapeutic combination is not evidence-based and no clear indications are provided with regard to the timing of antiplatelet suspension.[1] In elderly patients, the evaluation of the balance between safety and efficacy is further complicated by alterations in the geriatric domains of physical performance, cognitive impairment, and social support.

The comparison between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) has been tested in AF patients undergoing TAVR, demonstrating the non-inferiority of DOACs in terms of all-cause mortality, major and/or life-threatening bleeding and stroke.[36] Contrariwise, the worsening of renal function was more frequent with VKA compared to DOAC groups.[37] The choice of anticoagulant agents or anticoagulant/antiplatelet association after TAVR still represents a challenging problem due to the lack of robust and definitive evidence. The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After TAVR to Optimize Clinical Outcomes (GALILEO) trial has compared, in post-TAVR patients without other indications for anticoagulation, a treatment strategy with rivaroxaban at 10 mg daily plus aspirin vs. aspirin plus clopidogrel, both administered for the first 3 months post-procedure. The trial was interrupted due to increased mortality for both bleeding and thromboembolic events in the DOAC group.[38] However, it should be mentioned that the rivaroxaban-based strategy resulted more effective than an antiplatelet-based one in the prevention of subclinical leaflet-motion abnormalities.[39]

Recently, the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI) trial, which included patients with an established indication for long-term oral anticoagulation, confirmed a higher incidence of bleeding events among subjects receiving oral anticoagulation plus clopidogrel than those treated with OAC alone (34.6% vs. 21.7%).[40]

Current ongoing trials are trying to better define the most correct therapeutic approach: the Edoxaban Versus standard of care and their effects on clinical outcomes in patients having undergone Transcatheter Aortic Valve Implantation in Atrial Fibrillation (ENVISAGE-TAVI) is comparing edoxaban with VKAs in terms of efficacy and safety on NOAF/pre-existing AF patients,[41] while apixaban is under investigation in the trial Oral anti-Xa anticoagulation after trans-aortic valve implantation for AS (ATLANTIS), to demonstrate the superiority of this direct anticoagulant to the current standard of care in patients post-successful TAVR.[42]

This context clearly justifies the wide variations in treatment approaches among health centres, as real-world data from large registries reported that the majority of patients are not treated according to guideline recommendations, especially the elderly and frail ones.[27] It is essential to underline that real-world elderly patients sharply differ from those included in the clinical trials. Several conditions, including comorbidities, polypharmacotherapy, and various degrees of disability often represent exclusion criteria for entering in the studies,[43] despite they represent intrinsic features of the majority of outpatients and hospitals elderly patients, whose management is often determined by physician personal experience rather than by solid evidence in such heterogeneous and complex population.[44]

Key points: VKA should be preferred for long-term OAC therapy in AF patients with bioprosthesis; after the third month post-valve implantation, NOAC can be used. The addiction of antiplatelet agents to OAC in AF patients is not clearly recommended. Do not underestimate the risk for asymptomatic NOAF in elderly patients.

Antithrombotic therapy in patients with chronic kidney disease

One of the most frequent comorbidities observed in elderly patients undergoing TAVR is represented by chronic kidney disease (CKD), which seems to be inherently related to a more rapid AS progression.[45] Importantly, these two conditions share many factors involved in their pathophysiology, including advanced age, hypertension and diabetes. The alteration in bone metabolism deriving from kidney failure translates into calcification within the cardiovascular system, as also suggested by the augmented prevalence of severe AS in haemodialytic patients. Furthermore, the reduction in cardiac output due to AS results in altered kidney perfusion which in turn concurs to worsening renal function.[46,47]

The scientific literature has evaluated the clinical impact of CKD in patients undergoing TAVR, also focusing on the difficult decision-making process in elderly patients with several comorbidities, disability and frailty. CKD stages 3–5 patients undergoing TAVR show increased survival than those destined to pharmacological therapy, who further experience significant impairment in kidney function at 12 months.[48] Accordingly, a retrospective analysis on a cohort of Portuguese patients undergoing TAVR has demonstrated a subsequent improvement in kidney function, thus allowing to speculate on a presumable role exerted by the improvement in renal perfusion.[49]

Anyhow, in a recent analysis from the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) registry on 852 women undergoing TAVR, CKD emerged as being independently associated with negative outcomes, especially death, stroke, and major bleeding, with worse clinical events in the severe-CKD group than in the mild one.[50] Notably, although renal failure is often listed as exclusion criteria in randomized trials, thus resulting in limited evidence in end-stage CKD patients, recent studies suggest haemodialysis as an independent predictor of both short and long-term mortality in elderly undergoing TAVR. Indeed, periprocedural complications within 72 h occur six-fold more frequently than in the general population,[51] with 1-year mortality similar to that observed in the dialysis SAVR group, but significantly higher compared to non-dialysis patients.[52]

Coagulation abnormalities represent relevant causes of morbidity and mortality in CKD, since the coagulation system is altered due to uraemic metabolism-dependent abnormalities in platelet and vessel function leading to increased risk of both bleeding and thrombosis.[53] Moreover, few data are available regarding antiplatelet and anticoagulant agents in this specific setting, especially in the older frail subjects, which makes the choice of the antithrombotic strategy in CKD/haemodialysis patients undergoing TAVR a complex challenge. As a general consideration, it is important to underline that the most correct antiplatelet approach in CKD patients is still widely debated:

clopidogrel does not always provide a satisfactory response, aspirin is often linked to impaired antiplatelet effects, ticagrelor and prasugrel cannot be recommended in advanced CKD stages.[54] Contrariwise, efficacy and safety of anticoagulants have been tested in several trials, whose indications can be summarized as follows: VKA and DOACs are almost comparable in mild to moderate CKD, with the latter preferred in stages 1–3; a grey zone is represented by the end-stage renal failure, where warfarin constitutes the only anticoagulant treatment available; heparins in the haemodialytic patients still represents a debated choice.[55] Notably, recent evidence suggested that among patients with advanced CKD, apixaban showed lower safety and comparable efficacy compared to warfarin.[56]

With these premises in mind, for an optimal antithrombotic strategy in elderly CKD patients undergoing TAVR, it may be wise to consider a transitory DAPT in patients with low bleeding risk and an immediate SAPT strategy when the risk is high. Furthermore, in elderly advanced CKD patients undergoing TAVR with a concomitant indication for anticoagulant therapy, the scenario becomes even more complex and, due to the lack of specific recommendations, a personalized evaluation of the balance between haemorrhagic and thromboembolic risks becomes crucial. In this clinical setting, a careful assessment is requested to evaluate the opportunity of associating antiplatelet and anticoagulant agents.[54]

Moreover, clinical practice is burdened by several other issues in older CKD patients. First, VKA displays increased bleeding risk, especially in haemodialysis patients,[57] thus even more careful dosing is required, but the elderly population is not always able to monitor international normalized ratio (INR) values, especially in the contexts of poor social support and economic difficulties. Furthermore, older IV-V CKD stages and haemodialytic patients are generally excluded from clinical trials, thus the therapeutic strategies are mostly based on data derived from small observational or pharmacokinetic studies.[58] Finally, in multimorbid elderly patients on a large number of drugs, the accurate evaluation of the impact of concomitant therapies on kidney function is requested.

Key points: in CKD, consider transitory DAPT in low bleeding risk patients and immediate SAPT strategy when the bleeding risk is high. If concomitant indication for OAC coexists, the choice between VKAs and DOACs should be carefully evaluated according to CKD stage. Elderly multimorbid patients need personalized multidisciplinary evaluations.

TAVR in patients with autonomic dysfunction

It is well established that ageing is related to autonomic dysfunction, and several clinical conditions very frequent in the elderly are associated with inadequate autonomic responses to physiological stressors, including diabetes, alpha synucleinopathies like Lewy body dementia, Parkinson's disease and multiple system atrophy, chronic inflammatory conditions and heart failure.[59] Despite its complex presentation, the most common symptom of autonomic dysfunction is orthostatic hypotension, occasionally causing syncope. AS also presents with exertional dyspnoea and syncope. Recent reports have underlined the importance of evaluating all possible causes of syncope in patients with AS because the concurrence of autonomic failure might jeopardize management strategies, including TAVR.[59] Moreover, markers of cardiac autonomic dysfunction are strong predictors of mortality in post-infarction and heart failure patients. Recent evidence suggests that evaluation of autonomic function in patients with AS also yields independent prognostic information. In particular, severe autonomic failure seems to be a strong predictor of mortality in both symptomatic patients with AS undergoing invasive treatment and asymptomatic patients treated conservatively.[60] In another study on patients with severe AS undergoing TAVR, deceleration capacity of heart rate, a marker of autonomic function related to vagal tone, was a strong and independent predictor of 1-year mortality.[61] Time domain indices of heart rate variability are reduced in patients with severe aortic valve disease, especially in those with a progressed clinical class of heart failure. Moreover, a further reduction of heart rate variability time domain indices was observed 1 week after uncomplicated aortic valve replacement.[62] Interestingly, few studies have demonstrated that the type of surgery might have different influence over cardiac autonomic function in patient with aortic valve disease. In a comparative study, Compostella *et al.*[63] have shown that while SAVR led to profound depression of cardiac autonomic parameters, TAVR did not induce any significant deterioration of heart rate variability indexes. Similarly, Retzlaff *et al.*[64] have demonstrated that in contrast to patients undergoing conventional open surgery, fewer alterations of heart rate variability and baroreflex sensitivity were observed in patients with TAVR. In addition, it has been shown that TAVR improves cardiac sympathetic nerve activity measured through ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in severe aortic valve stenosis,[64] even within 2 weeks after the procedure.[65]

In terms of thrombotic risk, few studies have shown that orthostatic hypotension is associated with an increase in markers of coagulability, although the mechanisms have to be elucidated.[66] In elderly patients with Parkinson's disease, the thromboembolic risk seems to be increased by a combination of factors, which include immobility in more advanced stages, chronic inflammation and increased levels of homocysteine due to treatment with L-DOPA.[67]

Overall, these evidence indicate that autonomic dysfunction should be evaluated in all elderly patients with concomitant aortic valve disease to prevent concurrent complications, to predict the outcome of interventions and assess the risk of thrombotic events.

Key points: AS is related to impaired sympathetic nervous system activity, which is frequent in several age-related chronic diseases. TAVR seems to improve cardiac sympathetic nervous system dysfunction. Autonomic alteration is also related to higher thromboembolic risk, which may complicate the post-procedural management of patients undergoing TAVR.

Antithrombotic therapy and geriatric syndromes

Although it represents a contraindication to SAVR and despite TAVR may constitute the only therapeutic option to treat AS in this clinical condition, frailty has been associated with augmented risk of disability, institutionalization and mortality after TAVR.[68,69]

Physical performance impairments, very frequent in the elderly subjects, are often linked to increased risk of falls, one of the most dramatic events in this population, frequently resulting in negative outcome. Indeed, besides hip fracture, which constitutes a frequent

consequence of falls in older people, fall-related major haemorrhagic events represent a feared occurrence in the elderly, especially in those assuming antithrombotic therapy.[70] Furthermore, a lot of evidence has demonstrated the impact of frequently prescribed drugs, such as antidepressants, antihypertensive (especially diuretics), and digitalis, at increasing fall risk in people aged over 65.[71,72] In this clinical setting the concomitant prescription of antithrombotic therapy almost quadruples the occurrence of intracranial haemorrhage after trauma, thus posing relevant issues regarding the safety of managing post-TAVR patients.[73] Moreover, it has been reported the favourable functional impact of rehabilitation programmes in elderly patients undergoing TAVR.[74]

Mood disorders are also very frequent among elderlies, with relevant implications in terms of medical complications. In older patients undergoing surgery for AS, anxiety has been strongly associated with increased morbidity and mortality risks.[75] Similarly, patients with persisting depression suffer from a higher risk of mortality after surgery. Although the percutaneous procedure has recently demonstrated to progressively reduce depression and anxiety symptoms in elderly, compared to pre-TAVR status,[76] the antithrombotic management of patients undergoing TAVR may be complicated by the concomitant use of drugs for mood disorders, such as serotonin reuptake inhibitors, frequently associated with bleeding events and impaired haemostasis.[77]

Besides being considered a typical geriatric syndrome, with relevant impact in terms of medications and stress for both patients and caregivers,[78] delirium also represents a frequent complication in older patients after TAVR. Typical risk factors are represented by advanced age, male gender, cognitive impairment, malnutrition, sleep deprivation, polytherapy, and previous documented episodes. More specifically, post-TAVR delirium seems to be more frequent in patients with acute renal failure, carotid artery stenosis and undergoing transapical approach. Delirium is related to increased risk of falls and mortality following TAVR, thus further complicating the antithrombotic management of elderly AS patients.[79]

Blood disorders including anaemia, thrombocytopenia and acquired coagulative disorders are frequent among older TAVR recipients. Extensive evidence has detected an association between pre-existing anaemia, particularly common among people over 65 years,[80] and long-term mortality in elderly TAVR patients.[81] Data from the French national TAVI registry have demonstrated that the majority of patients experiences post-procedural haemoglobin drop ≥2 g/dL,[82] in line with the frequent recourse to post-operative blood transfusions, that may complicate the clinical course and therapeutic management[83] and is frequently associated with increased risk of acute kidney injury.[84] Many studies have reported transitory thrombocytopenia occurring in TAVR patients, with a restoration to baseline platelet levels within a week in the vast majority of them[81] and abnormality persistence in around a third of patients.[85]Post-procedural thrombocytopenia has been linked to augmented 1-year mortality and it is frequently complicated by bleeding events.[86] Taking into account the high prevalence of blood disorders in elderly patients, the above-mentioned conflicting data on the beneficial effects of DAPT in post-TAVR patients should be urgently updated in order to provide recommendations in such specific settings.

Finally, it is worth mentioning the burden of polypharmacotherapy in very elderly patients suffering from cardiovascular diseases, particularly when the efficacy of therapeutic approaches has not been proven.[87]

Key points: in elderly patients undergoing TAVR, be aware of fall risk and drug interactions that can alter haemostasis. Polypharmacotherapy, risk of delirium, and mood disorders should always be considered.

COVID-19 pandemic

The COronaVIrus Disease-2019 (COVID-19) pandemic, caused by the novel highly pathogenic severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first identified in December 2019, is rapidly spreading worldwide, with dramatic consequences in terms of morbidity and mortality, incalculable impact on global production systems and unpredictable evolution.[88] The symptomatic presentation is variable, including mild fatigue, fever, myalgia, headache, shortness of breath, dry cough, or diarrhoea, but it has the potential to develop acute respiratory disease syndrome, systemic inflammatory response syndrome (SIRS), and multiorgan failure with a more severe presentation among elderly, probably also due to intrinsic age-related features.[89–91] D-Dimer elevation, mild thrombocytopenia, prolongation of prothrombin time, and INR are common laboratory abnormalities, which seem to be associated with COVID-19 severity and may predispose to coagulation disorders.[92,93] Accordingly, a relevant proportion of deaths fulfilled the disseminated intravascular coagulation criteria and elevated antiphospholipid antibodies have been described in COVID-19 patients with limb and cerebral ischaemia.[94,95] Whether the thrombotic effect constitutes a consequence of cytokine storm that precipitates the SIRS or it is directly related to SARS-CoV2 pathogenicity remains unknown, anyhow consideration regarding antithrombotic management, even in the context of TAVR patients, may be necessary. Recently, the ESC has published the 'Guidance for the Diagnosis and Management of CV Disease during the COVID-19' also focusing on TAVR. It suggests to defer non-urgent procedures, giving priority to patients with syncope, high gradients and/or impaired systolic function and to prefer transfemoral approach in order to optimize the utilization of healthcare resources.[96] It is important to mention that some medications, such as lopinavir/ritonavir, may inhibit CYP3A4 activity thus producing potential drug interactions, and inducing physician to pay particular attention in molecules selection and dose (e.g. anticoagulants). Although remdesivir and tocilizumab also interfere with CYP3A4 activity, to date major drug–drug interactions with anticoagulants have not been reported, thus dose adjustments are not currently required.

Critical points and future perspective

The burden of valvular heart disease, especially AS in the elderly, is rapidly increasing and the recent developments leading to less invasive interventional strategies make it possible to tailor treatments to individual older patients. Furthermore, the management of valvular diseases in the elderly is probably one of the best examples of multidisciplinary teamwork in geriatric medicine: the ESC guidelines have established the 'Heart Team', a set of specialists (cardiologist, surgeon, anaesthetist, expert in care for the elderly, and even non-medical figures) in which the specific skills of all components are

Table 1 Main studies evaluating different antithrombotic regimens in TAVR patients

Study	Population and design	Outcomes	Results
Variation in post-TAVR antiplatelet therapy utilization and associated outcomes: Insights from the STS/ACC TVT Registry[8]	Multicentre study, 16 694 patients undergone transfemoral TAVR. Eighty-one percent were discharged on DAPT, 18% on SAPT. No use of anticoagulants.	Primary outcome: use of DAPT in patients without OAC. Secondary outcome: death, major bleeding, myocardial infarction, and stroke at 1 year.	DAPT patients were the majority and showed similar 1-year mortality risk compared to SAPT, as for stroke and MI incidence, but a significantly higher bleeding risk.
Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve (ARTE)[9]	RCT, 222 patients undergoing TAVR, comparing aspirin (80–100 mg/day) plus clopidogrel 75 mg/day (DAPT) vs. aspirin monotherapy (SAPT).	Primary outcome: death, myocardial infarction (MI), stroke, and life-threatening bleeding within 3 months after TAVR.	SAPT reduces occurrence of major adverse events in patients undergoing TAVR without increasing stroke or MI risks.
A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement (GALILEO)[38]	RCT, 1644 patients without indication for OAC, comparing rivaroxaban (10 mg for the first 3 months) plus aspirin (75–100 mg) vs. antiplatelet strategy (aspirin at a dose of 75–100 mg plus clopidogrel 75 mg per day for the first 3 months).	Primary efficacy outcome: death or thromboembolic events. Primary safety outcome: major life-threatening bleeding events.	The study was prematurely interrupted due to security issues. Rivaroxaban group suffered a higher risk of death, thromboembolic, and bleeding complications compared to antiplatelet one.
Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation (POPular TAVI EU)[40]	RCT, 313 patients receiving OAC for other clinical indication assigned in 1:1 ratio to receive clopidogrel for 3 months or no adjunctive therapy.	Primary endpoints: all bleeding and non-procedure-related bleeding over 12 months.	Patients treated with OAC plus clopidogrel showed a higher incidence of life-threatening bleeding events compared to patients on OAC monotherapy.
Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation in Atrial Fibrillation: ENVISAGE-TAVI AF Trial[41]	RCT, comparing edoxaban 60 mg daily to VKA (INR: 2.0–3.0 or 1.6–2.6) therapy in patients with an indication for OAC.	Primary endpoints: composite of all-cause death, myocardial infarction, ischaemic stroke, systemic thromboembolism, and valve thrombosis. Coprimary endpoint: major bleeding complications.	Ongoing
Oral anti-Xa Anticoagulation After Trans-Aortic Valve Implantation for Aortic Stenosis: The Randomized ATLANTIS Trial[42]	RCT, comparing standard therapeutic regimen (VKAs or DAPT/SAPT) vs. apixaban 5 mg b.i.d. or 2.5 mg b.i.d. strategy.	Primary endpoint: composite of thromboembolic and major bleeding events up to 1 year	Ongoing
The impact of chronic kidney disease in women undergoing transcatheter aortic valve replacement: Analysis from the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) registry[50]	Multinational, prospective registry of 852 women who completed 1-year follow-up. Patients were categorized into three eGFR-groups: no CKD, mild CKD; moderate/severe CKD	Primary safety endpoints: all-cause mortality, stroke, life-threatening bleeding, repeated procedure for valve-related dysfunction, at 30 days and 1 year.	CKD is an independent 1-year predictor of morbidity and mortality and other cardiovascular complications but did not affect the short-term results.
Meta-analysis Comparing Direct Oral Anticoagulants Versus Vitamin K Antagonists After Transcatheter Aortic Valve Implantation[36]	Meta-analysis of five eligible studies including 2569 patients with indication to OAC, comparing DOACs to VKAs.	Primary efficacy outcomes: all-cause death, stroke events. Primary safety outcome: major and/or life-threatening bleedings.	DOACs did not provide significant difference in all-cause mortality, major and/or life-threatening bleeding and stroke, compared to VKAs.
Impact of pre- and post-procedural anaemia on the incidence of acute kidney injury and 1-year mortality in patients undergoing transcatheter aortic valve implantation [from the French Aortic National CoreValve and Edwards 2 (FRANCE 2) Registry][82]	Data from 3472 patients were reported in the French national TAVI registry, divided into three groups according to post-procedural anaemia (Hb < 2 g/dL; Hb < 4 g/dL; and Hb > 4 g/dL).	Primary outcome: 1-year mortality and incidence of AKI.	Either pre- and post-procedural anaemia were correlated with AKI and 1-year mortality.

AKI, acute kidney injury; CKD, chronic kidney disease; DAPT, dual anti-platelet therapy; DOAC, direct oral anti-coagulant; Hb, haemoglobin; INR, international normalized ratio; MI, myocardial infarction; OAC, oral anti-coagulant; RCT, randomized controlled trial; SAPT, single antiplatelet therapy; TAVR, transcatheter aortic valve replacement; VKA, vitamin K antagonist.

combined in order to build a real comprehensive decision process and to choose the most appropriate treatment approach for each patient.

Nonetheless, TAVR still carries many issues concerning post-procedural optimal antithrombotic strategy to balance concomitant thromboembolic and bleeding risks. Despite the great progresses in the field obtained in the last decade, mainly related to the publications of retrospective studies and registry data, many critical points are still debated, and therefore recommendations from the guidelines do not provide sufficiently evidence-based indications (*Table 1*).

Anyhow, this field of scientific research is very active and the results of the ongoing trials will help to define the scenario more clearly.[97] The Trial to Assess the Safety and Efficacy of Prophylactic TicagrelOr With Acetylsalicylic Acid Versus CLopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular EMbolic Events During TAVI (PTOLEMAIOS, NCT02989558) is comparing DAPT with clopidogrel or ticagrelor in addition to acetylsalicylic acid on cerebrovascular events after TAVR, through transcranial Doppler ultrasound.[98] The impact of ticagrelor monotherapy, compared to clopidogrel plus acetylsalicylic acid, after TAVR is under test in the Safety Profile Evaluation of Ticagrelor Alone Compared to a Combination of Lysine Acetylsalicylate-Clopidogrel in the Context of Transcatheter Aortic Valve Implantation (TICTAVI, NCT02817789).[99]

In addition to the two above-mentioned major studies that are testing the usefulness of DOACs in patients undergoing TAVR with indication to anticoagulant therapy for other clinical conditions (ATLANTIS, NCT02664649 and ENVISAGE TAVI AF, NCT02943785), anticoagulation-based strategies in patients without indication for OAC are also under investigation, after the negative results of the GALIEO trial. Indeed, the Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement (ADAPT-TAVR, NCT03284827) trial is comparing edoxaban monotherapy vs. DAPT (aspirin and clopidogrel) on the incidence of leaflet thrombosis on cardiac CT imaging.[100]

The Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (AVATAR; NCT02735902) trial will assess the safety and efficacy of adding aspirin to OAC after TAVR in patients with indication for chronic anticoagulation.[101]

In AF patients undergoing TAVR and with absolute or relative contraindication to OAC, a non-pharmacological approach with left atrial appendage occlusion is currently assessed in the WATCHMAN for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement (WATCH-TAVR; NCT03173534) and the Comparison of Left Atrial Appendage Occlusion Versus Standard Medical Therapy in Patients in AF Undergoing TAVI (TAVI/LAAO; NCT03088098) trials.[102,103]

The spread of TAVR procedures worldwide highlights the need of dedicated clinical investigations on the antithrombotic management of complex patients suffering from concomitant chronic diseases and high grades of disability and frailty. Given the difficulties to design specific studies in this population, establishment of global registers from centres with greater experience in TAVR may help to collect evidence on these subpopulations.

Conclusive remarks

Elderly patients, who constitute the vast majority of people undergoing TAVR, represent a heterogeneous population, with highly variable characteristics and great vulnerability, suffering from several comorbidities and various degrees of disabilities. Since multimorbidity is often listed as an exclusion criterion in most of the research protocols, consensus documents and guidelines rarely provide ad hoc recommendations for managing complex cases, as demonstrated by the difficulties in choosing optimal antithrombotic therapy in TAVR patients when concomitant geriatric syndromes, as AF and/or CKD, occur.

In this scenario, a thorough assessment of possible ischaemic and bleeding complications and an attempt at attenuating these risks, also through behavioural measures, still remain the main challenges the physician has to face, awaiting for further evidence aiming to provide suitable indications for the complex real-life clinical practice.

Acknowledgements

Dr Leonardo Bencivenga has been supported by a research grant provided by the Cardiopath PhD programme.

Authors' contributions

L.B., I.S., M.E.P., and G.R. contributed to the conception of the work. L.B., I.S., M.E.P., K.K., G.C., B.P., M.A., and G.R. drafted the manuscript. L.B., A.C., N.F., D.G.F., and G.R. critically revised the manuscript and gave final approval. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest: none declared.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Roffi M, Alfieri O, Agewall S, Ahlsson A, Barbato E, Bueno H, Collet JP, Coman IM, Czerny M, Delgado V, Fitzsimons D, Folliguet T, Gaemperli O, Habib G, Harringer W, Haude M, Hindricks G, Katus HA, Knuuti J, Kolh P, Leclercq C, McDonagh TA, Piepoli MF, Pierard LA, Ponikowski P, Rosano GMC, Ruschitzka F, Shlyakhto E, Simpson IA, Sousa-Uva M, Stepinska J, Tarantini G, Tche D, Aboyans V. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38**: 2739–2786.
2. Ancona R, Comenale Pinto S. Epidemiology of aortic valve stenosis (AS) and of aortic valve incompetence (AI): is the prevalence of AS/AI similar in different parts of the world? *E-Journal of Cardiology Practice - Volume* **18**.
3. Kalich BA, Allender JE, Hollis IB. Medication Management of Patients Undergoing Transcatheter Aortic Valve Replacement. *Pharmacother J Hum Pharmacol Drug Ther* 2018; **38**: 122–138.
4. Bergmark BA, O'Donoghue ML, Murphy SA, Kuder JF, Ezhov M V., Ceška R, Gouni-Berthold I, Jensen HK, Tokgozoglu SL, Mach F, Huber K, Gaciong Z, Lewis BS, Schiele F, Jukema JW, Pedersen TR, Giugliano RP, Sabatine MS. An Exploratory Analysis of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition and Aortic Stenosis in the FOURIER Trial. *JAMA Cardiol.* Epub ahead of print April 2020. DOI: 10.1001/jamacardio.2020.0728.
5. Gulino S, Di Landro A, Indelicato A. Aortic Stenosis: Epidemiology and Pathogenesis. In: *Percutaneous Treatment of Left Side Cardiac Valves*. Springer International Publishing, 2018, pp. 245–252.
6. Tribouilloy C, Rusinaru D, Bohbot Y, Maréchaux S, Vanoverschelde J, Enriquez-Sarano M. How Should Very Severe Aortic Stenosis Be Defined in Asymptomatic Individuals? *J Am Heart Assoc* 2019; **8**: e011724.
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH,

DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Stevenson WG, Yancy CW. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the american college of cardiology/american heart association task force on practice guidelines. *Circulation*; **129**. Epub ahead of print June 2014. DOI: 10.1161/CIR.0000000000000031.

8. Sherwood MW, Vemulapalli S, Harrison JK, Dai D, Vora AN, Mack MJ, Holmes DR, Rumsfeld JS, Cohen DJ, Thourani VH, Kirtane A, Peterson ED. Variation in post-TAVR antiplatelet therapy utilization and associated outcomes: Insights from the STS/ACC TVT Registry. *Am Heart J* 2018; **204**: 9–16.
9. Rodés-Cabau J, Masson J-B, Welsh RC, Garcia del Blanco B, Pelletier M, Webb JG, Al-Qoofi F, Généreux P, Maluenda G, Thoenes M, Paradis J-M, Chamandi C, Serra V, Dumont E, Côté M. Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve. *JACC Cardiovasc Interv* 2017; **10**: 1357–1365.
10. Ciarambino T, Sansone G, Para O, Giordano M. Atrial fibrillation: all the elderly go hospitalized? A minireview. *J Gerontol Geriatr* 2020; **68**: 47–52.
11. Van Mieghem NM, Chieffo A, Dumonteil N, Tchetche D, Van Der Boon RMA, Buchanan GL, Marcheix B, Vahdat O, Serruys PW, Fajadet J, Carrié D, Colombo A, De Jaegere PPT. Trends in outcome after transfemoral transcatheter aortic valve implantation. *Am Heart J* 2013; **165**: 183–192.
12. Muscente F, De Caterina R. Risk of stroke after transcatheter aortic valve implant: The role of the new oral anticoagulants. *European Heart Journal, Supplement* 2019; **21**: B50–B51.
13. Alassar A, Soppa G, Edsell M, Rich P, Roy D, Chis Ster I, Joyce R, Valencia O, Barrick T, Howe F, Moat N, Morris R, Markus HS, Jahangiri M. Incidence and mechanisms of cerebral ischemia after transcatheter aortic valve implantation compared with surgical aortic valve replacement. *Ann Thorac Surg* 2015; **99**: 802–808.
14. Valvo R, Costa G, Tamburino C, Barbanti M. Antithrombotic Therapy in Transcatheter Aortic Valve Replacement. *Front Cardiovasc Med* 2019; **6**: 73.
15. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. *N Engl J Med* 2010; **363**: 1597–1607.
16. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith Transcatheter CR. Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019; **380**: 1695–1705.
17. Agnihotri A. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: Executive summary. *J Thorac Cardiovasc Surg* 2012; **144**: 534–537.
18. Dangas GD, Lefèvre T, Kupatt C, Tchetche D, Schäfer U, Dumonteil N, Webb JG, Colombo A, Windecker S, Ten Berg JM, Hildick-Smith D, Mehran R, Boekstegers P, Linke A, Tron C, Van Belle E, Asgar AW, Fach A, Jeger R, Sardella G, Hink HU, Husser O, Grube E, Deliargyris EN, Lechthaler I, Bernstein D, Wijngaard P, Anthopoulos P, Hengstenberg C. Bivalirudin Versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement the Randomized BRAVO-3 Trial. *J Am Coll Cardiol* 2015; **66**: 2860–2868.
19. Vivian GN, Susheel KK. Neurological Complications With TAVR - American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2019/01/25/09/12/neurological-complications-with-tavr#:~:text=In addition to clinically apparent,ischemic embolic lesions post-TAVR.&text=These studies have shown that,consistent with embolic showering events
20. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: A diffusion-weighted magnetic resonance imaging study. *Circulation* 2010; **121**: 870–878.
21. Muntané-Carol G, Urena M, Munoz-Garcia A, Padrón R, Gutiérrez E, Regueiro A, Serra V, Capretti G, Himbert D, Moris C, Sabaté M, Garcia del Blanco B, Ferreira-Neto AN, Coté M, Fischer Q, Couture T, Kalavrouziotis D, Rodés-Cabau J. Late Cerebrovascular Events Following Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2020; **13**: 872–881.
22. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y-H, McAnulty JH, Zheng Z-J, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 *Study*. *Circulation* 2014; **129**: 837–847.
23. Vora AN, Dai D, Matsuoka R, Harrison JK, Hughes GC, Sherwood MW, Piccini JP, Bhardwaj B, Lopes RD, Cohen D, Holmes DR, Thourani VH, Peterson E, Kirtane A, Kapadia S, Vemulapalli S. Incidence, Management, and Associated Clinical Outcomes of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Replacement: An Analysis From the STS/ACC TVT Registry. *JACC Cardiovasc Interv* 2018; **11**: 1746–1756.
24. Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, Jensen KT, Blanke P, Leetmaa T, Tang M, Krusell LR, Klaaborg KE, Christiansen EH, Terp K, Terkelsen CJ, Poulsen SH, Webb J, Bøtker HE, Nørgaard BL. Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. *J Am Coll Cardiol* 2016; **68**: 2059–2069.
25. Latib A, Naganuma T, Abdel-Wahab M, Danenberg H, Cota L, Barbanti M, Baumgartner H, Finkelstein A, LeGrand V, De Lezo JS, Kefer J, Messika-Zeitoun D, Richardt G, Stabile E, Kaleschke G, Vahanian A, Laborde JC, Leon MB, Webb JG, Panoulas VF, Maisano F, Alfieri O, Colombo A. Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis. *Circ Cardiovasc Interv*; **8**. Epub ahead of print April 2015. DOI: 10.1161/CIRCINTERVENTIONS.114.001779.
26. Siontis GCM, Praz F, Lanz J, Vollenbroich R, Roten L, Stortecky S, Räber L, Windecker S, Pilgrim T. New-onset arrhythmias following transcatheter aortic valve implantation: A systematic review and meta-analysis. *Heart* 2018; **104**: 1208–1215.
27. Guedeney P, Mehran R, Collet JP, Claessen BE, Ten Berg J, Dangas GD. Antithrombotic therapy after transcatheter aortic valve replacement. *Circulation: Cardiovascular Interventions*; **12**. Epub ahead of print 2019. DOI: 10.1161/CIRCINTERVENTIONS.118.007411.
28. Vlastra W, Jimenez-Quevedo P, Tchétché D, Chandrasekhar J, De Brito FS, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, Baan J, Tijssen JGP, De La Torre Hernandez JM, Dumonteil N, Sarmento-Leite R, Sartori S, Rosato S, Tarantini G, Lunardi M, Orvin K, Pagnesi M, Hernandez-Antolin R, Modine T, Dangas G, Mehran R, Piek JJ, Delewi R. Predictors, incidence, and outcomes of patients undergoing transfemoral transcatheter aortic valve implantation complicated by stroke from the center-collaboration. *Circ Cardiovasc Interv*; **12**. Epub ahead of print 2019. DOI: 10.1161/CIRCINTERVENTIONS.118.007546.
29. Mojoli M, Gersh BJ, Barioli A, Masiero G, Tellaroli P, D'Amico G, Tarantini G. Impact of atrial fibrillation on outcomes of patients treated by transcatheter aortic valve implantation: A systematic review and meta-analysis. *Am Heart J* 2017; **192**: 64–75.
30. Kalra R, Patel N, Doshi R, Arora G, Arora P. Evaluation of the Incidence of New-Onset Atrial Fibrillation after Aortic Valve Replacement. *JAMA Intern Med* 2019; **179**: 1122–1130.
31. Robert R, Porot G, Vernay C, Buffet P, Fichot M, Guenancia C, Pommier T, Mouhat B, Cottin Y, Lorgis L. Incidence, Predictive Factors, and Prognostic Impact of Silent Atrial Fibrillation After Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2018; **122**: 446–454.
32. Megaly M, Garcia S, Anzia LE, Morley P, Garberich R, Gornick CC, Lesser J, Sorajja P, Gössl M, Sengupta J. Detection of Atrial Fibrillation and Atrial Flutter by Pacemaker Device Interrogation After Transcatheter Aortic Valve Replacement (TAVR): Implications for Management. *J Invasive Cardiol* 2019; **31**: E177–E183.
33. Abubakar H, Yassin AS, Akintoye E, Bakhit K, Pahuja M, Shokr M, Lieberman R, Afonso L. Financial Implications and Impact of Pre-existing Atrial Fibrillation on In-Hospital Outcomes in Patients Who Underwent Transcatheter Aortic Valve Implantation (from the National Inpatient Database). *Am J Cardiol* 2018; **121**: 1587–1592.
34. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Esquivias GB, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal* 2016; **37**: 2893–2962.
35. Stefanini GG, Stortecky S, Meier B, Windecker S, Wenaweser P. Severe aortic stenosis and coronary artery disease. *EuroIntervention* 2013; **9**: S63–S68.
36. Ueyama H, Kuno T, Ando T, Briasoulis A, Fox J, Hayashida K, Takagi H. Meta-analysis Comparing Direct Oral Anticoagulants Versus Vitamin K Antagonists After Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2020; **125**: 1102–1107.
37. Mangner N, Crusius L, Haussig S, Woitek FJ, Kiefer P, Stachel G, Leontyev S, Schlotter F, Spindler A, Höllriegel R, Hommel J, Thiele H, Borger MA, Holzhey D, Linke A. Continued Versus Interrupted Oral Anticoagulation During Transfemoral Transcatheter Aortic Valve Implantation and Impact of

Postoperative Anticoagulant Management on Outcome in Patients With Atrial Fibrillation. *Am J Cardiol* 2019; **123**: 1134–1141.
38. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, de Backer O, Guimarães AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schäfer U, Seeger J, Tchétché D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020; **382**: 120–129.
39. de Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, Kini AS, Veien KT, Abdel-Wahab M, Kim WK, Balan P, van Mieghem N, Mathiassen ON, Jeger R V., Arnold M, Mehran R, Guimarães AHC, Nørgaard BL, Kofoed KF, Blanke P, Windecker S, Søndergaard L. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med* 2020; **382**: 130–139.
40. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, ten Berg JM. Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. *N Engl J Med*. Epub ahead of print March 2020. DOI: 10.1056/nejmoa1915152.
41. Van Mieghem NM, Unverdorben M, Valgimigli M, Mehran R, Boersma E, Baber U, Hengstenberg C, Shi M, Chen C, Saito S, Veltkamp R, Vranckx P, Dangas GD. EdoxabaN Versus standard of care and theIr effectS on clinical outcomes in pAtients havinG undergonE Transcatheter Aortic Valve Implantation in Atrial Fibrillation—Rationale and design of the ENVISAGE-TAVI AF trial. *Am Heart J* 2018; **205**: 63–69.
42. Collet JP, Berti S, Cequier A, Van Belle E, Lefevre T, Leprince P, Neumann FJ, Vicaut E, Montalescot G. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial. *Am Heart J* 2018; **200**: 44–50.
43. Bencivenga L, Komici K, Corbi G, Cittadini A, Ferrara N, Rengo G. The management of combined antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: A particularly complex challenge, especially in the elderly. *Frontiers in Physiology*; **9**. Epub ahead of print 2018. DOI: 10.3389/fphys.2018.00876.
44. Bencivenga L, Grieco F V., Femminella GD, de Lucia C, Komici K, Rengo C, Ferrara N, Rengo G. Management and Treatment of Cardiovascular Diseases in the Elderly. *Curr Pharmacogenomics Person Med* 2017; **15**: 1–9.
45. Marwick TH, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, Newby LK, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, Sarnak MJ, Banerjee D, Briguori C, Chang TI, Chen CL, deFilippi CR, Ding X, Ferro CJ, Gill J, Gössl M, Isbel NM, Ishii H, Jardine MJ, Kalra PA, Laufer G, Lentine KL, Lobdell KW, Lok CE, London GM, Małyszko J, Mark PB, Marwan M, Nie Y, Parfrey PS, Pecoits-Filho R, Pilmore H, Qunibi WY, Raggi P, Rattazzi M, Rossignol P, Ruturi J, Sabanayagam C, Shanahan CM, Shroff GR, Shroff R, Webster AC, Weiner DE, Winther S, Wiseman AC, Yip A, Zarbock A. Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. In: *Kidney International*. Elsevier B.V., 2019, pp. 836–849.
46. Hensey M, Murdoch DJ, Sathananthan J, Wood DA, Webb JG. Impact of Chronic Kidney Disease on Decision Making and Management in Transcatheter Aortic Valve Interventions. *Canadian Journal of Cardiology* 2019; **35**: 1188–1194.
47. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *The Lancet* 2013; **382**: 339–352.
48. Steinmetz T, Witberg G, Chagnac A, Green H, Sagie A, Rozen-Zvi B, Kornowski R. Transcatheter aortic valve implantation versus conservative treatment in chronic kidney disease patients. *EuroIntervention* 2018; **14**: e503–e510.
49. Calça R, Teles RC, Branco P, Gaspar A, Brito J, Nolasco T, Almeida MD, Neves JP, Mendes M, Machado DS, Weigert A. Impact of transcatheter aortic valve implantation on kidney function. *Arq Bras Cardiol* 2019; **113**: 1104–1111.
50. Bandyopadhyay D, Sartori S, Baber U, Cao D, Chandiramani R, Tchétché D, Petronio AS, Mehilli J, Lefèvre T, Presbitero P, Capranzaro P, Sardella G, Van Mieghem NM, Chandrasekhar J, Dumonteil N, Fraccaro C, Trabattoni D, Mikhail GW, Naber C, Kini A, Morice MC, Claessen BE, Chieffo A, Mehran R. The impact of chronic kidney disease in women undergoing transcatheter aortic valve replacement: Analysis from the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) registry. *Catheter Cardiovasc Interv*. Epub ahead of print 2020. DOI: 10.1002/ccd.28752.
51. Schymik G, Bramlage P, Herzberger V, Bergmann J, Conzelmann LO, Würth A, Luik A, Schröfel H, Tzamalis P. Impact of Dialysis on the Prognosis of Patients Undergoing Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2019; **123**: 315–322.
52. Kobrin DM, McCarthy FH, Herrmann HC, Anwaruddin S, Kobrin S, Szeto WY, Bavaria JE, Groeneveld PW, Desai ND. Transcatheter and surgical aortic valve replacement in dialysis patients: A propensity-matched comparison. In: *Annals of Thoracic Surgery*. Elsevier USA, 2015, pp. 1230–1237.
53. Lutz J, Menke J, Sollinger D, Schinzel H, Thürmel K. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant* 2013; **29**: 29–40.
54. Covic A, Genovesi S, Rossignol P, Kalra PA, Ortiz A, Banach M, Burlacu A. Practical issues in clinical scenarios involving CKD patients requiring antithrombotic therapy in light of the 2017 ESC guideline recommendations. *BMC Medicine*; **16**. Epub ahead of print September 2018. DOI: 10.1186/s12916-018-1145-0.
55. Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. *Clinical Cardiology* 2019; **42**: 774–782.
56. Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, Kaewput W, Pachariyanon P, Cheungpasitporn W. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis. *PACE - Pacing Clin Electrophysiol* 2018; **41**: 627–634.
57. Hughes S, Szeki I, Nash MJ, Thachil J. Anticoagulation in chronic kidney disease patients - The practical aspects. *Clinical Kidney Journal* 2014; **7**: 442–449.
58. Ghadban R, Flaker G, Katta N, Alpert MA. Anti-thrombotic therapy for atrial fibrillation in patients with chronic kidney disease: Current views. *Hemodialysis International* 2017; **21**: S47–S56.
59. Marigold JRG, Arias M, Vassallo M, Allen SC, Kwan JS. Autonomic dysfunction in older people. *Rev Clin Gerontol* 2011; **21**: 28–44.
60. Zuern CS, Rizas KD, Eick C, Vogtt MI, Bigalke B, Gawaz M, Bauer A. Severe autonomic failure as a predictor of mortality in aortic valve stenosis. *Int J Cardiol* 2014; **176**: 782–787.
61. Duckheim M, Bensch C, Kittlitz L, Götz N, Klee K, Groga-Bada P, Mizera L, Gawaz M, Zuern C, Eick C. Deceleration capacity of heart rate predicts 1-year mortality of patients undergoing transcatheter aortic valve implantation. *Clin Cardiol* 2017; **40**: 919–924.
62. Jung J, Heisel A, Butz B, Fries R, Schieffer H, Tscholl D, Schäfers H-J. Factors influencing heart rate variability in patients with severe aortic valve disease. *Clin Cardiol* 1997; **20**: 341–344.
63. Compostella L, Russo N, Compostella C, Setzu T, D'Onofrio A, Isabella G, Tarantini G, Iliceto S, Gerosa G, Bellotto F. Impact of type of intervention for aortic valve replacement on heart rate variability. *Int J Cardiol* 2015; **197**: 11–15.
64. Retzlaff B, Wessel N, Riedl M, Gapelyuk A, Malberg H, Bauernschmitt N, Kurths J, Bretthauer G, Bauernschmitt R. Preserved autonomic regulation in patients undergoing transcatheter aortic valve implantation (TAVI)-a prospective, comparative study. *Biomed Tech* 2011; **56**: 185–193.
65. Kadoya Y, Zen K, Tamaki N, Ito N, Kuwabara K, Yamano M, Yamano T, Nakamura T, Matsushima S, Oka K, Numata S, Yaku H, Matoba S. Early effects of transcatheter aortic valve replacement on cardiac sympathetic nervous function assessed by 123I-metaiodobenzylguanidine scintigraphy in patients with severe aortic valve stenosis. *Eur J Nucl Med Mol Imaging* 2020; **47**: 1657–1667.
66. Isma N, Sutton R, Hillarp A, Strandberg K, Melander O, Fedorowski A. Higher levels of von Willebrand factor in patients with syncope due to orthostatic hypotension. *J Hypertens* 2015; **33**: 1594–1601.
67. Tana C, Lauretani F, Ticinesi A, Prati B, Nouvenne A, Meschi T. Molecular and clinical issues about the risk of venous thromboembolism in older patients: A focus on parkinson's disease and parkinsonism. *International Journal of Molecular Sciences*; **19**. Epub ahead of print May 2018. DOI: 10.3390/ijms19051299.
68. Thongprayoon C, Cheungpasitporn W, Kashani K. The impact of frailty on mortality after transcatheter aortic valve replacement. *Annals of Translational Medicine*; **5**. Epub ahead of print March 2017. DOI: 10.21037/atm.2017.01.35.
69. Arnold S V., Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, Zajarias A, Thourani VH, Green P, Rodés-Cabau J, Beohar N, Mack MJ, Leon MB, Cohen DJ. Predictors of poor outcomes after transcatheter aortic valve replacement results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 2014; **129**: 2682–2690.
70. Bond AJ, Molnar FJ, Li M, Mackey M, Man-Son-Hing M. The risk of hemorrhagic complications in hospital in-patients who fall while receiving antithrombotic therapy. *Thrombosis Journal* 2005; **3**: 1.
71. Institute of Medicine (US) Division of Health Promotion and Disease Prevention. Falls in Older Persons: Risk Factors and Prevention. In: *The Second Fifty Years: Promoting Health and Preventing Disability*. 1992, pp. 263–284.
72. Andersen CU, Lassen PO, Usman HQ, Albertsen N, Nielsen LP, Andersen S. Prevalence of medication-related falls in 200 consecutive elderly patients with hip fractures: a cross-sectional study. *BMC Geriatr* 2020; **20**: 121.

73. Hohmann N, Hohmann L, Kruse M. The impact of combined use of fall-risk medications and antithrombotics on injury severity and intracranial hemorrhage among older trauma patients. *Geriatr Nurs (Minneap)* 2014; **35**: 20–25.
74. Pressler A, Förschner L, Hummel J, Haller B, Christle JW, Halle M. Long-term effect of exercise training in patients after transcatheter aortic valve implantation: Follow-up of the SPORT:TAVI randomised pilot study. *Eur J Prev Cardiol* 2018; **25**: 794–801.
75. Williams JB, Alexander KP, Morin JF, Langlois Y, Noiseux N, Perrault LP, Smolderen K, Arnold S V., Eisenberg MJ, Pilote L, Monette J, Bergman H, Smith PK, Afilalo J. Preoperative anxiety as a predictor of mortality and major morbidity in patients aged >70 years undergoing cardiac surgery. *Am J Cardiol* 2013; **111**: 137–142.
76. Bäz L, Wiesel M, Möbius-Winkler S, Westphal JG, Schulze PC, Franz M, Dannberg G. Depression and anxiety in elderly patients with severe symptomatic aortic stenosis persistently improves after transcatheter aortic valve replacement (TAVR). *Int J Cardiol. Epub ahead* of print 2020. DOI: 10.1016/j.ijcard.2020.03.021.
77. Halperin D, Reber G. Influence of antidepressants on hemostasis. *Dialogues in Clinical Neuroscience* 2007; **9**: 47–59.
78. Grover S, Avasthi A. Clinical practice guidelines for management of delirium in elderly. In: *Indian Journal of Psychiatry*. Medknow Publications, 2018, pp. S329–S340.
79. Tilley E, Psaltis PJ, Loetscher T, Davis DH, Harrison SL, Kim S, Keage HAD. Meta-analysis of Prevalence and Risk Factors for Delirium After Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2018; **122**: 1917–1923.
80. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. *Blood* 2004; **104**: 2263–2268.
81. De Larochellière H, Puri R, Eikelboom JW, Rodés-Cabau J. Blood Disorders in Patients Undergoing Transcatheter Aortic Valve Replacement: A Review. *JACC: Cardiovascular Interventions* 2019; **12**: 1–11.
82. Arai T, Morice MC, O'Connor SA, Yamamoto M, Eltchaninoff H, Leguerrier A, Leprince P, Laskar M, Iung B, Fajadet J, Prat A, Lièvre M, Donzeau-Gouge P, Chevreul K, Teiger E, Lefèvre T, Gilard M. Impact of pre- and post-procedural anemia on the incidence of acute kidney injury and 1-year mortality in patients undergoing transcatheter aortic valve implantation (from the French Aortic National CoreValve and Edwards 2 [FRANCE 2] Registry). *Catheter Cardiovasc Interv* 2015; **85**: 1231–1239.
83. Vavuranakis M, Kalogeras K, Kolokathis AM, Vrachatis D, Magkoutis N, Siasos G, Oikonomou E, Kariori M, Papaioannou T, Lavda M, Moldovan C, Katsarou O, Tousoulis D. Antithrombotic therapy in TAVI. *Journal of Geriatric Cardiology* 2018; **15**: 66–75.
84. Nuis RJ, Rodés-Cabau J, Sinning JM, Van Garsse L, Kefer J, Bosmans J, Dager AE, Van Mieghem N, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Dumont E, Van Domburg RT, De Jaegere PP. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2012; **5**: 680–688.
85. Flaherty MP, Mohsen A, Moore JB, Bartoli CR, Schneibel E, Rawasia W, Williams ML, Grubb KJ, Hirsch GA. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2015; **85**: 118–129.
86. Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, Torguson R, Kirtane AJ, Minha S, Badr S, Pendyala LK, Loh JP, Okubagzi PG, Fields JN, Xu K, Chen F, Hahn RT, Satler LF, Smith C, Pichard AD, Leon MB, Waksman R. Acquired thrombocytopenia after transcatheter aortic valve replacement: Clinical correlates and association with outcomes. *Eur Heart J* 2014; **35**: 2663–2671.
87. Mostaza JM, Lahoz C, Salinero-Fort MA, Cardenas J. Cardiovascular disease in nonagenarians: Prevalence and utilization of preventive therapies. *Eur J Prev Cardiol* 2019; **26**: 356–364.
88. World Health Organization W. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. *WHO Director General's speeches* 2020; 4.
89. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng G, Yuen K-Y, Chen R, Tang C, Wang T, Chen P, Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–1720.
90. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, Komici K, Mazzarella G, Parrella R, Bianco A. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res* 2020; 1–10.
91. Bencivenga L, Rengo G, Varricchi G. Elderly at time of COronaVIrus disease 2019 (COVID-19): possible role of immunosenescence and malnutrition. *GeroScience* 2020; 1–4.
92. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, Zhu Y, Liu Y, Wang X, Wang L. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol* 2020; **92**: 791–796.
93. Boccia M, Aronne L, Cclia B, Mazzeo G, Ceparano M, D'Agnano V, Parrclla R, Valente T, Bianco A, Perrotta F. COVID-19 and coagulative axis: Review of emerging aspects in a novel disease. *Monaldi Archives for Chest Disease* 2020; **90**: 271–276.
94. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; **18**: 844–847.
95. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med* 2020; **382**: e38.
96. European Society of cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. 2020; 1–115.
97. Lugo LM, Romaguera R, Gómez-Hospital JA, Ferreiro JL. Antithrombotic therapy after transcatheter aortic valve implantation. *Eur Cardiol Rev;* **15**. Epub ahead of print 2020. DOI: 10.15420/ecr.2019.10.
98. NCT02989558. A Trial to Assess the Safety and Efficacy of Prophylactic TicagrelOr With Acetylsalicylic Acid Versus CLopidogrel With Acetylsalicylic Acid in the Development of Cerebrovascular EMbolic Events During TAVI. Https://clinicaltrials.gov/show/nct02989558.
99. NCT02817789. Safety Profile Evaluation of TICagrelor Alone Compared to a Combination of Lysine Acetylsalicylate-Clopidogrel in the Context of Transcatheter Aortic Valve Implantation (TAVI). Https://clinicaltrials.gov/show/nct02817789.
100. NCT03284827. Anticoagulant Versus Dual Antiplatelet Therapy for Preventing Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement. https://clinicaltrials.gov/show/NCT03284827.
101. Cayla G, Piot C, Levy G, Rivalland F, Leclerq F, Macia J-C, Schmutz L, Maupas E, Robert G. Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (1:1) (AVATAR).
102. NCT03088098. Comparison of Left Atrial Appendage Occlusion vs Standard Medical Therapy in Patients in AF Undergoing TAVI. https://clinicaltrials.gov/show/NCT03088098.
103. NCT03173534. WATCH-TAVR, WATCHMAN for Patients With Atrial Fibrillation Undergoing Transcatheter Aortic Valve Replacement. Https://clinicaltrials.gov/show/nct03173534.